DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
12420 Parklawn Drive, Room 2032 Rockville, MD 20857	6/16/2025-6/27/2025*
	FEI NUMBER 3004762406

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Hugues Dolgos, CEO

FIRM NAME	STREET ADDRESS
NerPharMa S.r.l.	Bldgs 65 and 71, Viale Pasteur 10
CITY, STATE, ZIP CODE, COUNTRY Nerviano, Milan, 20014 Italy	TYPE ESTABLISHMENT INSPECTED Drug Manufacturer

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

OBSERVATION 1

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile did not include adequate validation of the aseptic and sterilization process.

Specifically,

A) Inherent and corrective interventions and the times/durations in which they occur, are not always documented within batch production records as required by procedure TB021, Injectables: Allowed Interventions During Aseptic Processing on (b) (4) Line, Version: 3. There is no assurance the maximum number of times and durations they are performed during routine production are accurately simulated during media fills.

B) Media fills are performed using a split batch approach, where some units of the batch are transferred to the (b) (4) (to represent the (b) (4) process) and the remaining vials are filled as (b) (4) This media fill approach is not representative of routine operations.

C) During Aseptic Process Simulations, Step (b) (4) states to simulate the sampling "without taking any vials from the filling line". However, during the December 2023 and the subsequent six media fills performed in 2024 for the vial filling line, vials were removed (b) (4) for performing weight checks. The following are amounts of media that could not be incubated due to performing weight checks:

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Media Fill Batch Number / Date	Filling Weight Check
(b) (4)	

D) The initial (b) (4) vials filled on day 1 and the initial (b) (4) vials filled on day 2 of each media fill are removed for sterility testing. These vials are not subject to the inverted incubation condition required by media fill.

Media Fill Batch Number	# of Vials for Sterility testing
(b) (4)	

E) During the inspection, we reviewed videos of smoke studies conducted in 2024 for the vial filling line (b) (4) . This line is for all U.S. injectables. We observed poor aseptic practice. We also observed your smoke studies did not provide assurance that unidirectional airflow (first air) was always maintained. The following were noted:

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1. No smoke studies (at rest or in operation) were performed for the (b) (4) Grade A LAF (b) (4) to assure unidirectional airflow was maintained. These (b) (4) were used to transport (b) (4) products and all sterile components or accessories required during aseptic filling operations.

2. Video #16 "Stopper Loading" (in operation) showed (b) (4) of stoppers. We observed an updraft of airflow near a metal frame in the ceiling below the HEPA filter and above the area where stopper bags were cut open for loading.

3. Video #6 "At rest (b) (4) " (at rest) showed an updraft of airflow inside the extended Grade A (b) (4) enclosure. This updraft of airflow was observed near the ceiling light fixture. (b) (4) is used to sterilize (b) (4) for the (b) (4) of (b) (4) vials.

4. Video #24 "Filled (b) (4) From the Line to the LAF (b) (4) (in operation) showed vials being moved from the filling line to the LAF (b) (4) We observed the operator blocked first air to the vials in the (b) (4) by placing his hand, arm, and (b) (4) station mechanical arm over vials.

5. We watched video #31 "Removal stopper stuck in the feeding chute" (in operation). We observed an operator blocked first air by placing his hand directly over open vials while removing a stuck stopper from the feeding chute. The impacted vials were not rejected.

6. Video #29 "Removal of stuck/broken/inverted vials after dosing group" (in operation) showed an operator blocked first air by placing his hand directly over open vials. The impacted vials were not rejected.

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7. Video #22 " Removal (b) (4) seal stuck in the (b) (4) (in operation) showed an operator removed stuck seals. We observed this operator blocked first air to the sterile seals and (b) (4) by placing his hands and arms directly over sterile seals inside the (b) (4)

8. Video #16 "Stopper Loading" (in operation) showed (b) (4) of stoppers. We observed the operator partially blocked first air to the stopper bowl. We also observed the operator used quick shaking motion to empty the stopper bag.

9. Video #10 "At rest (b) (4) machine" (at rest) showed the airflow inside and around the (b) (4) machine. This machine is for the (b) (4) products. We observed laminar airflow leaving the extended Grade A (b) (4) area, hitting the Grade B wall, and creating an upward swirl of airflow. Your firm did not have assessment for the observed turbulent airflow.

F) The vial filling line (b) (4) was modified in 2024 with the addition of the (b) (4) The following were noted:

1. Procedure for (b) (4) integrity testing has not been validated to assure leaks, tears, or defects can be adequately detected. The firm stated no integrity failures have been observed since the installation and qualification of (b) (4) in March 2024. On 16-June-2025, we watched a demonstration of the (b) (4) integrity testing. The first (b) (4) tested failed integrity test.

2. The (b) (4) Leak Teste IN/GLT/01 is used to test (b) (4) The IQ/OQ/OQ have not been performed to adequately qualify the (b) (4) leak tester.

3. Procedure TD186 section 4.3 states the (b) (4) can be sterilized for a maximum of (b) (4) times. No validation has been performed to assign the (b) (4) sterilization cycles. The numbers of sterilization cycles are based on vendor's recommendation.

4. Each (b) (4) is not assigned a unique identification number to assure traceability.

G) During the inspection, we observed aseptic operators used goggles that had numerous open holes and therefor had exposed skin during filling line set-up and aseptic processing. Holes in goggles create pathways for contaminations to enter the cleanroom environment affecting product sterility.

OBSERVATION 2

Aseptic processing areas are deficient regarding the system for monitoring environmental conditions.

Specifically,

A) Procedure TF002, Injectables: Microbial Environmental Monitoring of Classified Areas, Version: 44, requires all Grade A and B microbial recoveries to be identified down to the Genus and Species level. Since January 2023 there have been approximately 457 instances where microorganisms have been recovered from the Grade A and B areas during environmental and personnel monitoring. Of the 457 instances, the organisms have only been identified 55 times (approximately 88% not identified).

B) Active air sampling is not performed within the Grade A vial filling line (b) (4) in Room (b) (4) due to insufficient space to place active air samplers.

C) You did not place the non-viable particle (NVP) monitoring probes in representative Garde A

locations where the product was exposed. We noted the following:

2. The NVP monitoring probe was approximately (b) (4) from one of the (b) (4) (b) (4) station where (b) (4) vials were positioned in a (b) (4) and awaited (b) (4) to the LAF (b) (4)

2. The NVP monitoring probe was approximately (b) (4) from the (b) (4) (b) (4) station where (b) (4) vials were positioned in a (b) (4) and awaited (b) (4) to the LAF (b) (4)

OBSERVATION 3

Aseptic processing areas are deficient regarding the system for cleaning and disinfecting the room and equipment to produce aseptic conditions.

Specifically,

A) The disinfectant efficacy studies are deficient for the following reasons:

3. The studies were not performed using representative microorganisms. Gram negative, yeast, and spore forming microorganisms have not been evaluated as part of the studies for disinfectants (b) (4)
Additionally, gram negative and yeast microorganisms have not been evaluated as part of the study for (b) (4)

2. Disinfectant efficacy studies have not been performed on the surface (b) (4) found inside the Grade A filling line (b) (4)

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B) There is a lack of (b) (4) qualification for the Grade A vial line (b) (4) and adjacent cleanrooms. For example:

3. The biological indicator (BI) and chemical indicator (CI) locations were not determined by risk assessment. Their locations were based on vendor recommendations.

2. There is a lack of written procedure or records available to show the cleanrooms were appropriately prepared to receive (b) (4) (b) (4) is not effective unless rooms are adequately prepared. For example, the rooms should be clean and have ≥(b) (4) C temperature and <(b) (4) relative humidity.

C) Performance of sanitization of the Grade A Vial Filling Line (b) (4) was not documented until 05-July-2024. There is no assurance that cleaning was performed prior to that.

D) The logbook which documents the sanitization of the Grade A Vial Filling Line (b) (4) does not list which disinfectant agent was used to sanitize the line.

E) Contact times are not documented on cleaning records for the Grade A/B Room (b) (4) and the vial filling machine (b) (4) to ensure the minimum contact time for each solution used has been met.

OBSERVATION 4

Written records are not always made of investigations into unexplained discrepancies and the failure of a batch or any of its components to meet specifications.

Specifically,

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A) Deviations opened in response to microbial action limit excursions within the Grades A and B filling area are not closed in a timely time. For example, deviation DP035/2025 was opened on 03-April-2025 due to settle plate action limit excursions in the Room (b) (4) (all Grade B areas) with the following results:

Location	Specification	First Plate Result	Second Plate Result	Third Plate Result
(b) (4)				

To date, the investigation for this deviation has not been performed because the microorganisms recovered from the environmental monitoring sample action level excursions have not been identified.

B) Out-of-Limit #OOL.CM.031.25 was opened for microbial alert limit excursion of (b) (4) bacterial and (b) (4) mold (b) (4) CFU total) recovered on the settle plate in Grade B area location Room (b) (4) dated 04-April-2025. This OOL was closed on 13-June-2025 without identifying the microorganisms. On 23-June-2025, during the current FDA inspection, the mold was identified as *Penicillium nothofagi*, however, the other (b) (4) bacteria were not submitted for identification.

C) (b) (4) Injection (b) (4) mg/vial lot #(b) (4) failed (b) (4) visual inspection with 26.27% major category defects rejected. The

specification for major category defects is no more than (b) (4)%. A reinspection was performed only on the (b) (4) vials which were originally rejected for presence of product on the inner surface of the vial (major defect). The reinspection of these vials resulted in 286 of these vials being rejected while the remaining (b) (4) vials being deemed acceptable and returned to the batch for release. Deviation DP015/2025 does not identify why the original acceptable vials were not re-inspected and if a new specification should be used for the re-inspection. This lot was released to the US Market.

D) The three out-of-specification (OOS) investigations for (b) (4) batches #(b) (4) were not closed in a timely time. The following OOS show the date of initiation and the date of closure:

Batch Number	OOS Number	Open Date	Close Date
(b) (4)	DP RS/231/2024/04	20-Dec-2024	04-April-2025
	DP FS/231/2025/01	13-Jan-2025	5-June-2025
	DP FS/231/2025/02	04-Feb-2025	10-June-2025

OBSERVATION 5

Your firm failed to establish adequate written procedures for production and process controls designed to assure that the drug products have the identity, strength, purity, and quality that they are purported or represented to possess.

Specifically,

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A) Vial sizes used for qualification of visual inspectors for visual inspection are not justified. For example:

1. The qualification kit for (b) (4) product in (b) (4) vial is a (b) (4) mL size, however, the only product produced at the facility that is (b) (4) and in (b) (4) vial (b) (4) (b) (4) is a (b) (4) mL vial size.

2. The qualification kit for (b) (4) product in a clear vial is a (b) (4) mL size, however, vial sizes for (b) (4) in a clear vial are (b) (4) mL, (b) (4) mL, (b) (4) mL, and (b) (4) mL.

3. The qualification kit for (b) (4) product in a clear vial is (b) (4) mL in size, however, vial sizes for (b) (4) product (both aseptically processed and terminally sterilized) ar (b) (4) mL, (b) (4) mL, (b) (4) mL, and (b) (4) mL.

B) The visual inspection kits, used to qualify operators for (b) (4) visual inspection, do not contain all defects that are required to identify and reject during visual inspection. These include, but not limited to:

1. (b) (4) in a clear vial: vial not conform (critical), missing seal (critical), seal not conform (critical), missing stopper (critical), empty vial (major), product on the wall (major), and presence of product on the vial (externally) (major), which are defect types for visual inspection.

2. (b) (4) in (b) (4) vial: vial not conform (critical), missing seal (critical), empty vial (major), presence of product on the stopper (major), dirty stopper (major).

3. Solution in clear vial: particles (critical), non conform vial (critical), product appearance not conforms (major), product appearance not conforms (major), broken or damaged stopper

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(major), and dirty stopper (major).

C) The visual inspection kits for (b) (4) product do not contain particles, fibers, and glass of a known size.

D) Visual inspectors are required to be able to identify the defect vials during qualification and record the category of defect (such as critical, major, and minor). The qualification records do not indicate what specific defect (such as glass, fibers, etc.) was observed for each of the categorized defect.

OBSERVATION 6

The responsibilities and procedures applicable to the quality control unit are not in writing and fully followed.

Specifically,

A) The Quality Unit review of records does not ensure the accuracy of the reported data. For example, during filling of (b) (4) Injectio (b) (4) ng/vial lot (b) (4) intervention (b) (4) (adjustment of (b) (4) occurred on 16-Jan-2025 from (b) (4) requiring a Grade A gown monitoring. The operator identified as performing the intervention "(b) (6)" was not the same operator that received the required Grade A gown monitoring.

B) A CAPA was not implemented in response to Deviation DP015/2025 to update the visual inspection kits for (b) (4) drug product to contain a vial that represents the defect presence of product on the stopper, which is a major defect.

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OBSERVATION 7

Appropriate controls are not exercised over computers or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel.

Specifically,

Your production and quality unit (QU) did not review electronic raw data or audit trails to ensure data integrity prior to batch release or completion of maintenance activities. For example, your operators obtained and printed passing results for (b) (4) integrity tests. Your operators did not record or print the failing results. Impacted production systems included, but were not limited to, the (b) (4) Integrity Tester (IN/FI/07), the Grade A and B Integrated Environmental Monitor System (b) (4) IN/PA/07), and the (b) (4) Grade A (b) (4) non-viable particle counter (NVPC) (b) (4)

OBSERVATION 8

Laboratory controls do not include the establishment of scientifically sound and appropriate sampling plans and test procedures designed to assure that components and drug products conform to appropriate standards of identity, strength, quality and purity.

Specifically,

The firm's kinetic turbidimetric LAL bacterial endotoxin test for finished products is inadequate.

The bacterial endotoxin test for finished products requires the testing of (b) (4) sample (b) (4) containers of finished product (b) (4) I reviewed SOP and found the test procedure deficient in that it did not allow for adjustment of the Maximum Valid Dilution (MVD) of (b) (4) sample which can lead to false negative results due to the potential for

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diluting a unit potentially containing harmful levels of endotoxins with other units containing lower, less harmful, levels of endotoxins. The current MVD calculation is based on (b) (4) container of finished product determined by method validation and did not accurately reflect the MVD of the (b) (4) sample during routine testing for product release for stability testing. The firm's management confirmed it has been the practice since endotoxin test was first performed by QC.

***DATES OF INSPECTION**

6/16/2025(Mon), 6/17/2025(Tue), 6/18/2025(Wed), 6/19/2025(Thu), 6/20/2025(Fri), 6/23/2025(Mon), 6/24/2025(Tue), 6/25/2025(Wed), 6/26/2025(Thu), 6/27/2025(Fri)

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